```
=> s glycine transport inhibitor?
        140522 GLYCINE
        651695 TRANSPORT
        931041 INHIBITOR?
L1          40 GLYCINE TRANSPORT INHIBITOR?
               (GLYCINE(W)TRANSPORT(W)INHIBITOR?)

=> s alzheimers
L2        2719 ALZHEIMERS

=> s l1 and l2
L3           1 L1 AND L2

=> d cbib abs

L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2005 ACS on STN
2002:570709   Document No. 137:124979  Preparation of diaryl-enyne glycine
     derivatives as glycine transport inhibitors
     for treatment of schizophrenia, cognitive dysfunction, and Alzheimer's
     disease.  Egle, Ian; Frey, Jennifer; Isaac, Methvin (NPS Allelix Corp.,
     Can.).  U.S. US 6426364 B1 20020730, 19 pp.  (English).  CODEN: USXXAM.
     APPLICATION: US 2000-704225 20001101.  PRIORITY: US 1999-PV162986
     19991101.
GI
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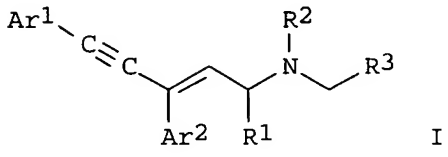

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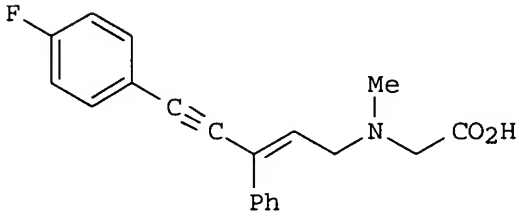

II

AB Title compds. I [wherein Ar1 and Ar2 = independently (un)substituted (hetero)aryl; R1 = H or alkyl; R2 = H, alkyl, or benzyl; R3 = CO2R, CONRR', CONH(OH), COSR, SO2NRR', PO(OR)(OR'), or tetrazolyl; R and R' = independently H or alkyl; and salts, solvates, or hydrates thereof] were prepared in several steps from aryl iodides, alkynes, and sarcosines. For example, Me phenylpropiolate was coupled with TMSC.tplbond.CH in the presence of Pd(OAc)2 and tris(2,6-dimethoxyphenyl)phosphine to give 1-methoxycarbonyl-2-phenyl-4-trimethylsilyl-1-buten-3-yne (86%), which was reduced to the alc. using DIBAL-H (71%). Bromination, followed by addition of t-Bu sarcosine•HCl, afforded the tertiary amine (58% over 2 steps). Desilylation with K2CO3 in MeOH (99%), arylation with 4-fluoroiodobenzene in the presence of Pd(PPh3)4, CuI, and NEt3 (77%), and deesterification with HCO2H (90%) gave the pentenyne II. I are active as GlyT-1 inhibitors and bind to the glycine sites on the NMDA receptor (no data). Thus, I are useful for the treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease (no data).

```
=> s glycine
L4      140522 GLYCINE

=> s l4 and l2
L5          18 L4 AND L2

=> d tot ti

L5   ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Memantine blocks α7* nicotinic acetylcholine receptors more potently
     than N-methyl-D-aspartate receptors in rat hippocampal neurons

L5   ANSWER 2 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Preparation of aryltriazoles as glycine transporter inhibitors.

L5   ANSWER 3 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Inhibition of nicotinic acetylcholine receptors by apolipoprotein
     E-derived peptides in rat hippocampal slices

L5   ANSWER 4 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Preparation of (benzyloxy)phthalimides as inhibitors of monoamine oxidase
     B

L5   ANSWER 5 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Chemical properties and physiological activities of synnemata of Beauveria
     bassiana

L5   ANSWER 6 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Transgenic animals models of Alzheimer's disease with mutant human amyloid
     precursor protein and screening anti-Alzheimer's agents

L5   ANSWER 7 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Preparation of 1-phenyl-1-(arylsulfonyl)cyclohexanes for treatment of
     Alzheimer's disease

L5   ANSWER 8 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Macrocycles useful in the treatment of alzheimer's disease

L5   ANSWER 9 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Preparation of peptide-related hydrazine derivatives for treating
     Alzheimer's disease

L5   ANSWER 10 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Preparation of diaryl-enyne glycine derivatives as
     glycine transport inhibitors for treatment of schizophrenia,
     cognitive dysfunction, and Alzheimer's disease

L5   ANSWER 11 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Hormone replacement therapy compositions containing estradiol and an
     isoflavone for use in the treatment of various postmenopausal
     pathophysiological disorders

L5   ANSWER 12 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   D-cycloserine, a partial NMDA receptor-associated glycine-B site
     agonist, enhances reversal learning, but a cholinesterase inhibitor and
     nicotine has no effect

L5   ANSWER 13 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Excitatory amino acid-induced changes in amygdaloid and hippocampal APP
     mRNA expression: effect of selective antagonists

L5   ANSWER 14 OF 18  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Time-related cortical amino acid changes after basal forebrain lesion: a
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microdialysis study

L5 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI High-level expression and in vitro mutagenesis of a fibrillogenic 109-amino-acid C-terminal fragment of Alzheimer's-disease amyloid precursor protein

L5 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Hyperpurification of paired helical filaments reveals elevations in hydroxyproline content and a core structure related peptide fragment

L5 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Isolation and chemical characterization of Alzheimer's disease paired helical filament cytoskeletons: differentiation from amyloid plaque core protein

L5 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Purification, ultrastructure, and chemical analysis of Alzheimer disease amyloid plaque core protein

=> d 15 hit

L5 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB The N-methyl-D-aspartate (NMDA) receptor antagonist memantine is an approved drug for treatment of Alzheimer's disease (AD). Other such treatments are cholinesterase inhibitors and nicotinic acetylcholine receptor (nAChR)-sensitizing agents such as galantamine. The present study was designed to test whether memantine exerts any effect on the cholinergic system, in particular the Ca2+-conducting α7* nAChR, in cultured hippocampal neurons. Memantine caused a concentration-dependent reduction of the amplitudes of whole-cell currents evoked by the α7* nAChR-selective agonist choline (10 mM) or by N-methyl-D-aspartate (NMDA) (50 μM) plus **glycine** (10 μM). It also inhibited tonically activated NMDA receptors. Memantine was more potent in inhibiting α7* nAChRs than NMDA receptors; at -60 mV, the IC50 values for memantine were 0.34 and 5.1 μM, resp. Consistent with an open-channel blocking mechanism, memantine-induced NMDA receptor inhibition was voltage and use-dependent; the Hill coefficient (nH) was .apprx.1. Memantine-induced α7* nAChR inhibition had an nH < 1 and showed a variable voltage dependence; the effect was voltage-independent at 0.1 μM, becoming voltage-dependent at ≥1 μM. Thus, memantine interacts with more than one class of sites on the α7* nAChRs. One is voltage-sensitive and therefore likely to be within the receptor channel. The other is voltage-insensitive and therefore likely to be in the extracellular domain of the receptor. It is suggested that blockade of α7* nAChRs by memantine could decrease its effectiveness for treatment of AD, particularly at early stages when the degrees of nAChR dysfunction and of

L5 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
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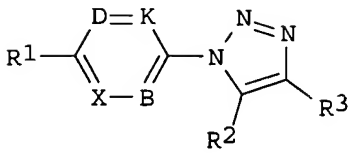

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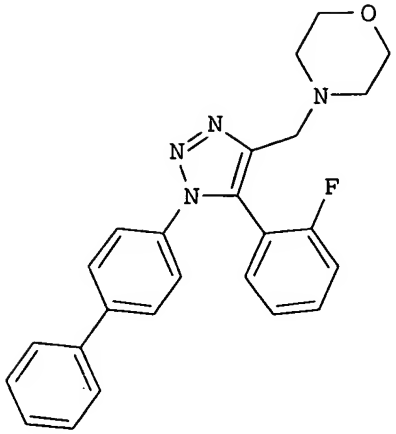

II

AB Title compds. [I; X, B, K, D = CH, N; R1 = H, A, halo, (CH2)nHet, (CH2)nAr, cycloalkyl, CF3, NO2, cyano, C(NH)NOH, OCF3; R2 = (CH2)nHet, (CH2)nAr, cycloalkyl, CF3; R3 = H, (CH2)nCO2R5, (CH2)nCOHet, CHO, (CH2)nHet, etc.; A = alkyl, alkoxy, alkenyl, alkoxyalkyl; n = 0-5; Ar = (substituted) Ph; Het = (substituted) (unsatd.) (aromatic) mono- or bicyclic heterocyclyl, heteroatom-containing organic residue], were prepared for treatment of schizophrenia, depression, dementia, Parkinson's disease, Alzheimer's disease, Lewy Body Dementia, Huntington's disease, Tourette syndrome, fear, learning and memory restrictions, neurodegenerative illnesses and other cognitive impairments, as nicotine dependence, and pain (no data). Thus, title compound (II) was prepared in several steps using 4-bromophenylhydrazine hydrochloride, Et (2-fluorobenzoyl)acetate, PhB(OH)2, and morpholine.

=> d 10 12 cbib abs

L5 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2002:570709 Document No. 137:124979 Preparation of diaryl-enyne **glycine** derivatives as **glycine** transport inhibitors for treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease. Egle, Ian; Frey, Jennifer; Isaac, Methvin (NPS Allelix Corp., Can.). U.S. US 6426364 B1 20020730, 19 pp. (English). CODEN: USXXAM. APPLICATION: US 2000-704225 20001101. PRIORITY: US 1999-PV162986 19991101.

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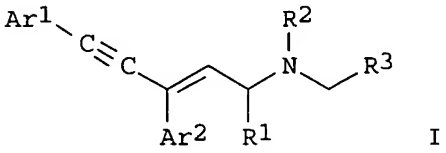

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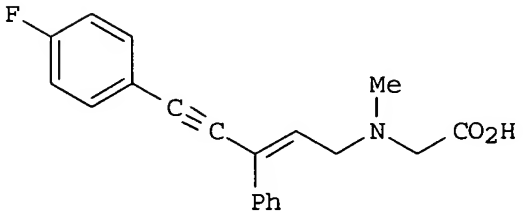

II

AB Title compds. I [wherein Ar1 and Ar2 = independently (un)substituted (hetero)aryl; R1 = H or alkyl; R2 = H, alkyl, or benzyl; R3 = CO2R, CONRR', CONH(OH), COSR, SO2NRR', PO(OR)(OR'), or tetrazolyl; R and R' = independently H or alkyl; and salts, solvates, or hydrates thereof] were prepared in several steps from aryl iodides, alkynes, and sarcosines. For example, Me phenylpropiolate was coupled with TMSC.tplbond.CH in the presence of Pd(OAc)2 and tris(2,6-dimethoxyphenyl)phosphine to give 1-methoxycarbonyl-2-phenyl-4-trimethylsilyl-1-buten-3-yne (86%), which was reduced to the alc. using DIBAL-H (71%). Bromination, followed by addition of t-Bu sarcosine•HCl, afforded the tertiary amine (58% over 2 steps). Desilylation with K2CO3 in MeOH (99%), arylation with 4-fluoroiodobenzene in the presence of Pd(PPh3)4, CuI, and NEt3 (77%), and deesterification with HCO2H (90%) gave the pentenyne II. I are active as GlyT-1 inhibitors and bind to the **glycine** sites on the NMDA receptor (no data). Thus, I are useful for the treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease (no data).

L5 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
1999:2158 Document No. 130:218089 D-cycloserine, a partial NMDA receptor-associated **glycine**-B site agonist, enhances reversal learning, but a cholinesterase inhibitor and nicotine has no effect. Riekkinen, Paavo, Jr.; Ikonen, Sami; Riekkinen, Minna (Department of Neurology, Canthia Building, University of Kuopio, Kuopio, FIN-70211, Finland). NeuroReport, 9(16), 3647-3651 (English) 1998. CODEN: NERPEZ. ISSN: 0959-4965. Publisher: Lippincott Williams & Wilkins.

AB The present study examined the efficacy of single and combined treatments with an anticholinesterase, tetrahydroaminoacridine, nicotine and a **glycine**-B site partial agonist, D-cycloserine, in alleviating the water maze reversal learning defect induced by a medial septal lesion. D-cycloserine (3 and 10 mg/kg) improved reversal learning. Tetrahydroaminoacridine (1 and 3 mg/kg) and nicotine (0.1 and 0.3 mg/kg) had no effect on reversal learning. A combination of

tetrahydroaminoacridine 3 mg/kg or nicotine 0.3 mg/kg and D-cycloserine 10 mg/kg was not more effective than D-cycloserine 10 mg/kg alone in improving reversal learning. This suggests that stimulation of NMDA mechanisms may more effectively improve in medial septal-lesioned rats reversal learning processes than stimulation of cholinergic activity. The data support the development ant testing of compds. that may enhance NMDA receptor activation for use in the treatment of Alzheimer's disease.

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